(npeoc, npc and nps) with specific reactions (deprotection reactions), allegedly does not reasonably provide enablement for any type of protecting groups and deprotection reagents. It is alleged that the specification does not enable a person of skill in the art to which it pertains, or with which it is mostly connected, to make and use the invention commensurate in scope with these claims because the specification fails to give adequate direction and guidance as to the means of making combinatorial libraries using any type of protecting groups to protect any reactive functional groups using deprotection reagents. The Office Action states that the specification discloses the criterion for selection of deprotection reagents and that the sequence of deprotection reactions are specific or predetermined based on the stability of the protection groups. The Office Action alleges that the working examples are directed to the use of specific protecting groups and deprotection reagents or conditions and the breadth of the claims is open ended regarding the use of protecting groups, deprotection reaction conditions, and the order of the deprotection reactions. It is alleged that the art is inherently unpredictable because the use of protecting groups in a specific position may be unstable during the deprotection conditions, and result in unwanted reactions to occur. The Office Action concludes that it would take undue trials and errors to practice the claimed invention. This rejection is respectfully traversed.

RELEVANT LAW

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of 35 U.S.C. §112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469

USPQ 367 (CCPA 1971)(emphasis added).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require **undue** experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

Applying the above factors to the instant claims, applicant respectfully submits that as described in detail below, it would not require undue experimentation to practice the claimed methods. Furthermore, as described in detail below, it is contrary to the purpose for which the patent system exists to require limitation of the claims to specific protecting groups disclosed and exemplified in the specification. Thus it would be unfair, unduly limiting and contrary to public policy that the cliams be so limited.

Scope of the claims

Claim 4, and claims 11-16 dependent thereon, are directed towards a process for generating a combinatorial library, comprising the steps of:

(a) preparing a plurality of immobilized molecules selected from a nucleoside and a nucleotide; wherein each molecule contains 3 to 10 reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups on each immobilized molecule are independently removable under at least three different conditions; and

(b) removing each blocking group and derivatizing the resulting reactive moiety in a preprogrammed, regioselective manner; wherein each member of the plurality of immobilized molecules is uniquely

derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial library."

Thus the claims are directed towards a process for generating a combinatorial library which is described in the specification in detail by disclosing all the steps involved. Each step of the process is described and taught in the subject specification (see pages 7-10). The specification, including the working examples, describe in great detail preparation of immobilized oligonucleotides by phosphoramidite method and disclose modifications to this strategy for extension to other oligonucleotide synthesis methods such as phosphotriester method (pages 11, 14-20). Various blocking groups for the reactive moieties in the molecules on phosphate and nucleoside bases are well characterized in the instant application and are well known to those with skill in the art, as are the deprotecting reagents for selective orthogonal deprotection (see pages 12-13). Furthermore the specification discloses stability of various protecting groups under the reaction conditions of orthogonal deprotection and cites a large number of articles, to describe protecting groups for reactive moieties in oligonucleotide synthesis. Therefore the claim 4, and claims 11-16 dependent thereon, are directed towards a process for generating a combinatorial library which is described in the specification.

The level of skill in the art is high

The level of skill in this art is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art.

Knowledge of those of skill in the art

At the time of the effective filing date of this application and before, a skilled artisan knew various protecting groups and deprotection reagents and conditions for use in nucleotide/nucleoside synthesis. Further, there is a large body of literature directed to the use and stability of various protecting groups under different reaction conditions. Selective removal of various protecting groups by using deprotection reagents is also well recorded in the art and known

to those of skill in the art.

The articles cited in the specification, of record in this application and attached hereto describe various protecting groups, including but not limited to, benzoyl, 4-methoxybenzoyl, pivaloyloxymethyl, allyloxycarbonyl, dialkylformamidine, benzoylpropionyl, 5-pentenoyl, isobutyryl and Fmoc group as discussed below for reactive functionalities in nucleotide synthesis. For example, protection of the carbohydrate 5' and/or 3'- hydroxy functions with protecting groups, including but not limited to, **trityl, acetyl, benzoylpropanoyl**; phosphate protection with **β-cyanoethyl, chlorophenyl**; and protection of the amino function on bases with **dimethylaminomethylene, acyl** is discussed in extensive details in the article published by Amarnath *et al.*, Chemical Reviews, **1977**, 77, 183-217. The protecting groups are categorized as acid labile, base labile and groups removable under neutral conditions. The reference describes reagents and conditions for deprotection of the protecting groups, for example 2,4-dinitrobenzenesulfenyl protecting group on 5'-hydroxy site of nucleosides can be removed by thiophenol in phenol.

An extensive review published by E. Sonveaux, *Bioorg. Chem.*, **1986,** 14, 274-325, discusses several protecting groups, including but not limited to, various **acyl groups, DmTr and pixyl,** for use in different oligonucleotide synthesis methods for individual bases and for 3'- and 5'-hydroxy groups.

An article by Reese, C. B., *Tetrahedron,* **1978,** 34, 3143-79, reviews various protecting groups, including but not limited to **benzoyl, p-anisoyl** for -OH functionalities and for the bases.

Watkins *et al.* in *J Am. Chem. Soc.,* **1982,** 104, 5702-08, have described use of **benzyloxycarbonyl** group removable under neutral hydrogenolysis conditions for base protection in oligonucleotide synthesis.

Gioeli *et al.* in *J. Chem. Soc. Chem. Commun.,* **1982,** 672-74, have described **Fmoc group** removable by basic reagents such as aqueous ammonia, piperidine, ethanolamine or morpholine, in the 5'-*O*-Fmoc-2'-deoxythymidine having orthogonal deprotection properties described in the instant application.

Kharasch *et al. J. Amer. Chem. Soc.,* **1953,** 75, 2658-60, have described **2,4-dinitrophenylsulfenyl (dnps) group** in the dnps ethyl ester which reveals

selective deprotection properties with deprotection reagents described in the instant application.

Several articles cited in the application on page 13 disclose phosphate and base protection groups and deprotection reagents.

In addition, a large body of publications, not cited in the application, describe protecting groups for nucleoside bases. Some exemplary publications are listed below.

U.S. Patent Nos. 5,763,599 and 5,652,358, describe **phenoxyacetyl, benzoyl, isobutyroyl, p-(t-butyl)benzoyl and p-(t-butyl)phenylacetyl** protecting group for nucleotide bases.

Koster et al., Tetrahedron 37, 363-369, and Ti *et al.* J. Am. Chem. Soc. 1982, 104: 1316-1319, report several **acyl protecting groups** for use in oligonucleotide synthesis. Comparative rates of deacylation of various acyl protecting groups in MeOH/NaOH mixture are also reported.

Rasmussen *et al.* J. Am. Chem. Soc. 1967, 89(21): 5439-45, disclose **pivaloyloxymethyl protecting group** removable under mildly basic conditions, for adenine.

Hayakawa *et al.* J. Am. Chem. Soc. 1990, 112: 1691-1696, describe **allyloxycarbonyl (AOC) protecting group** for nucleoside bases. AOC group can be removed by palladium(O) catalyzed reaction under mild conditions.

Vu *et al.* Tetrahedron Letters, 1990, 31, 7269-7272, describe **dialkylformamidine and isobutyryl** protection of nucleosides. Deprotection can be achieved under mild basic conditions.

Dreef-Tromp *et al.* Tetrahedron Letters, 1990, 31, 427-430, describe **2-(*tert*-butyldiphenylsilyloxymethyl)benzoyl protecting group** removable under neutral conditions by fluoride ion.

U.S. Patent No. 5,614,622 describe the use of **5-Pentenoyl** moiety as nucleoside amino protecting group in oligonucleotide synthesis. It can be deprotected by chemoselective removing agents for example, halogens in water or pyridine/alcohol or by nonchemoselective removing agents such as aqueous ammonium hydroxide or alcoholic ammonia.

Caruthers *et al.* Nucleosides & Nucleotides, 4(1&2), 95-105, have

described various **amidine protecting groups** which can be removed under basic condition, for nucleoside bases.

Letsinger *et al.* J. Am. Chem. Soc. 1969, 91:12: 3356-59, describe **β-benzoylpropionyl and benzoylformyl** for -OH protection of nucleosides and **isobutyloxycarbonyl** for -NH_2 protection during oligonucleotide synthesis. These can be removed under neutral conditions.

Vinogradov *et al.* Tetrahedron Letters 1993, 34, 5899-5902, describe **isopropoxyacetal group** for the protection of the exocyclic amine of the nucleic bases. Deprotection was achieved under basic conditions.

Kamimura *et al.* Tetrahedron Letters 1983, 24, 2775-2778, reported **diphenylcarbamoyl group** for protection of 6-O and **propionyl group** for protection on amino group in guanine. It was removed by ammonia + pyridine.

McBride *et al.* Tetrahedron Letters 1983, 24, 2953-56, reported **N-methyl-2-Pyrrolidine amidine** group as deoxynucleoside protecting group and removal was achieved by ethylenediamine:phenol.

Ogilvie *et al.* Tetrahedron Letters 1982, 23, 2615-18, describe **Levulinyl group** for amino protection in nucleosides and hydrazine as deprotection reagent.

Froehler *et al.* Nucleic Acid Research 1983, 11, have reported **dialkylformamidine protecting group** removable with ammonia, for N protection in deoxyadenosine.

In addition several protecting groups used in organic synthesis are described in "Protecting Groups in Organic Synthesis" by T. W. Greene.

Based on the disclosure of the instant specification and the information available in the art regarding protection/deprotection chemistry, a skilled artisan would be able to select at least three different protecting groups removable under at least three different conditions for use in the claimed process. For example, 3' and 5'-OH protection by a pixyl group (removed under acidic conditions), base protection with bezyloxycarbonyl group (removed under reductive conditions) and phosphate protection with o-chlorophenyl group (removed with $(n\text{-butyl})_4NF$)) represent one possible set of protecting groups removable under selective and orthogonal conditions. Therefore, it is respectfully submitted that based on the teachings and guidance in specification and the

knowledge of those of skill in the art, one can readily select those groups and reagents that meet the criteria for selective orthogonal deprotection for making combinatorial libraries per the instant claims.

The amount of direction and guidance presented, teachings in the specification and presence of working examples

The specification describes synthesis of oligomers for sequence specific selective and orthogonal deprotections and for subsequent derivatizations by the use of differently base and/or phosphate protected building blocks (Scheme 1, page 7-8). The specification describes and exemplifies various phosphate and base protecting groups, including but not limited to, nps, chlorophenyl, β-cyanoethyl, levulinic acid ester and DMTr. The specification also discloses their stability during deprotection reactions. For example, the specification page 13, lines 7-19, recites various phosphate protecting groups in the following paragraph:

> The phosphate protection with the p-chlorophenyl group e.g. is stable with reagent II in contrast to the β-cyanoethyl group (Hsiung, H.M., *Tetrahedron Lett.,* **1982,** 23, 5119-22). The phosphate protection with the o-chlorophenyl group e.g. is stable with 0.5M hydrazine reagent (Watkins, B.E., Kiely, J. S., Rapoport, H., *J Am. Chem. Soc.,* **1982,** 104, 5702-08). The phosphate protection with the 2,5-dichlorophenyl group e.g. is stable with strong acids as p-toluenesulfonic acid in methylene chloride/methanol (Himmelsbach, F., Schulz, B.S., Trichtinger. T., Ramamurthy, C., Pfleiderer, W,. *Tetrahedron,* **1984,** 40, 59-72). During the deprotection of R^{4B} no removal of the new substituents at ①-④ iis desired. The o--chlorophenyl group e.g. allows deprotection with 4-nitrobenzaldoximate without affecting benzoic acid ester and nps amide bonds (Heikkila, J., Balgobin, N., Chattopadhyaya, J., *Acta Chem. Scand.* , **1983,** B37, 857-62). Further the o-chlorophenyl group e.g. is easily removable with $(n\text{-butyl})_4NF$ (Reese, C.B., Titmas, R.C., Yau, L., *Tetrahedron Lett.,* **1978,** 2727-30). Under these conditions acetic acid ester, trityl ether bonds and the nucleoside base protection with the acetyl or benzoyl groups remain intact (Ogilvie, K.K., *Can.J.Chem.,* **1973,** 51, 3799-3807).

The specification at page 14, line 1-13 recites the use of nps protecting group:

> The rate of base deprotection in nps base protected nucleosides was found to be significantly influenced by the deprotection reagent (thiocresolate concentration and solvents). The rate of deprotection in 0.02M thiocresolate in pyridine decreases as follows: 2'-deoxy-N^2-nps-

> guanosine (G_d^{nps}) > > 2'-deoxy-N^4-nps-cytidine (C_d^{nps}) > > 2'-deoxy-N^6-nps-adenosine (A_d^{nps}). It would seem to be difficult to identify reagents leading to a reversion of this order to obtain e.g. nps protected cytosine and guanine in the presence of nps deprotected adenine moieties. But such a deprotection state could be achieved by selective deprotection of the C^{nps} and G^{nps} moieties, followed by reprotecting them with groups, stable with thiocresolate reagent. Finally A^{nps} can be deprotected with this reagent. In yet another approach, this protection scheme can be obtained by using the suitably protected nucleotide building blocks during oligomer synthesis.

The specification at page 14, line 23 through page 15, line 8 recites the use of chlorophenyl, β-cyanoethyl, levulinic acid ester and nps groups:

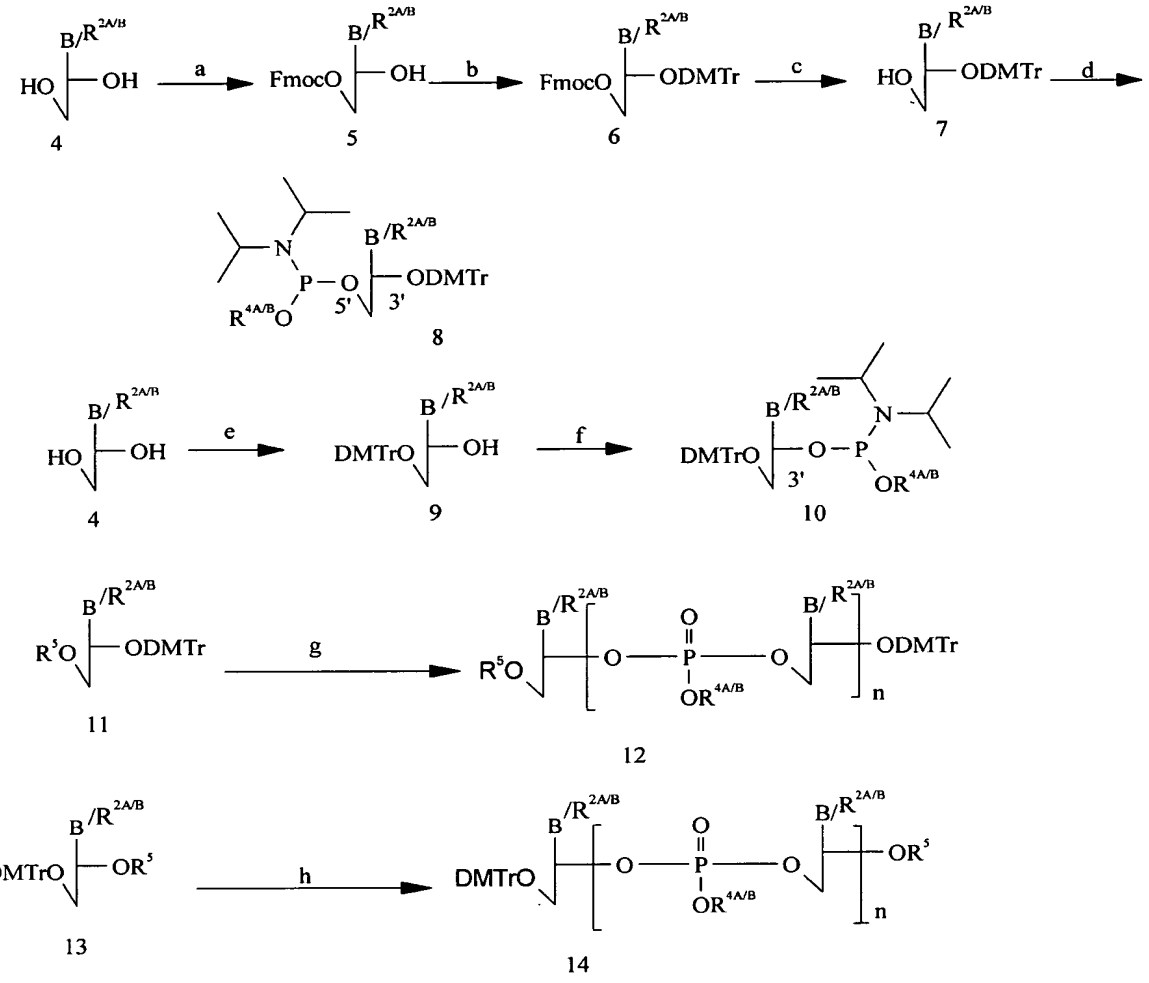
> For the phosphtriester method, chloro substituted phenyl groups and the ß-cyanoethyl group were successfully used as phosphate protection groups (Amarnath, V., Broom, A. D. *Chem. Rev.* **1977**, 77, 183-217; Reese, C. B., *Tetrahedron,* **1978,** 34, 3143-79). The levulinic acid ester and the npeoc/npe base protection are stable during the reaction conditions of the phosphotriester method (Himmelsbach, F., Schulz, B.S., Trichtinger, T., Ramamurthy, C., Pfleiderer, W., *Tetrahedron,* **1984,** 40, 59-72; van Boom, J.H., Burgers, P.M.J., *Tetrahedron Lett.,* **1976,** 4875-78). The nps base protection has been successfully used during the oligonucleotide synthesis by the phosphotriester approach (Heikkila, J., Balgobin, N., Chattopadhyaya. J., *Acad Chem. Sci.,* **1983,** B37, 857-62).

The specification at page 15, lines 11-20, further discloses the use of levulinic acid ester and DMTr groups:

> In addition, if the oligomer (e.g. **3** in scheme 1) is connected at its 3'-OH or 5'-OH group to the CPG via a levulinic acid ester bridge (cleavable with neutral hydrazine reagent IV) instead of the trityl ether bridge in **3**, a simplified 3'-5' as well as 5'-3' directed DNA syntheses would be available, keeping the advantage of multiselective deprotections, with the trityl moiety for easy detection and as a "purification handle" (Sinha, N.D., Biernat, J., Koster, H. *Tetrahedron Lett.,* 1983, 24, 5843-46; Sinha, N.D., Biernat, J., McManus, J., Koster, H. *Nucleic Acids Res.,* **1984,** 12, 4539-57; Sonveaux, E. *Bioorg. Chem.,* **1986,** 14, 274-325).
> For syntheses by the phosphoamidite method, amidites, whose 5'-OH or 3'-OH groups respectively are protected with the 4,4'-dimethoxytrityl (DMTR) group, are used.

Reaction scheme 3 on page 16, and reproduced below, discloses the use of Fmoc and DMTr protecting groups for 5' and 3'-OH groups.

SCHEME 3



a: selective 5'-OH protection. b: tritylation with DMTr chloride. c: 5'-OH deprotection, e.g. with *tert*-butyl amine reagent II (table 1) or with triethyl amine reagent. d: phosphitylation. e: selective 5'-OH protection with DMTr chloride. f: phosphitylation. g: 5'-3' directed oligonucleotide synthesis with **11** and **8.** h: 3'-5' directed oligonucleotide synthesis with **13** and **10** R^5: CPG----- $CH_2COCH_2CH_2CO$-(support anchored levulinyl group); n, B, B^R, $B^{R2A/B}1$, $R^{4A/B}$,

$R^{4A/B}$: see Scheme 1.

The specification at page 18, line 14, through page 19, line 10, discusses stability of nps protecting group:

> The following findings demonstrate the feasibility of this extension of the synthetic strategy with the levulinic acid ester bridge. The base protection of nucleosides protected with the 2-nitrophenylsulfenyl (nps) group is rather stable with strongly acidic solutions (Heikkila, J., Balgobin, N., Chattopadhyaya, J., *Acta Chem. Scand,* **1983,** B37, 857-62). We found that stability against depurination in 80% acetic acid decreases as follows: 2'deoxy-N^6-nps-adenosine (A_d^{nps}) >> 2'-deoxy-N^2-nps-guanosine (G_d^{nps}) > 2'-deoxy-N^2isobutyryl-guanosine (G_d^{ib}) >> 2'-deoxy-N^6-benzoyl-adenosine (A_d^{bz}); G_d^{ib} and A_d^{bz} are exposed to strong acids in every elongation cycle in the standard DNA synthesis process (Sinha, N.D., Biernat, J., Koster, H., *Tetrahedron Lett.,* **1983,** 24, 5843-46; Sinha, N.D., Biernat, J., McManus, J., Koster, H., *Nucleic Acids Res.,* **1984,** 12, 4539-57; Sonveaux, E., *Bioorg. Chem.,* **1986** 14, 274-325). In accordance with Heikkila, J. et al. *(Acta Chem.Scand.,* **1983,** B37, 857--62). A_d^{nps} does not depurinate with 80% acetic acid, although the main depurination problem in standard DNA synthesis is caused by the A_d^{bz} units. 2'-Deoxy-*N*^{4}-nps-cytidine (C_d^{nps}) is stable with 80% acetic acid.

Further specification on page 24, lines 9-15 discloses that Fmoc and dnps groups can be used under the reaction conditions of orthogonal deprotection:

> The Fmoc group in the 5'-*O*-Fmoc-2'-deoxythymidine (Gioeli, C., Chattopadhyaya, J.B., *J. Chem. Soc. Chem. Commun.,* **1982,** 672-74) showed orthogonal deprotection properties with I-IV (table 1) and the 2,4-dinitrophenylsulfenyl (dnps) group in the dnps ethyl ester (Kharasch, N., McQuarrie, D.P., Buess, C.M., *J. Amer. Chem. Soc.,* **1953,** 75, 2658-60) reveals comparable selective deprotection properties with reagents I-IVa to the 2-nitrophenylsulfenyl (nps) group in the nps amide moiety.

The specification describes, in an exemplary embodiment, the use of deprotecting reagents to deblock the blocking groups under selective and orthogonal conditions. For example, see specification page 9, lines 15-27:

Table 1. Selective and orthogonal deprotection at oligomer 3.

Deprotection at linkage in 3	*Reaction*		*Deprotection reagent*
①	detritylation	I:	80% acetic acid
②	decyanoethylation	II:	tertbutyl amine/ pyridine 1/9 (v/v)
③	base deprotection	III:	p-thiocresole in pyridine/DMF 3/7 (v/v): 3mmol/ ml
④	hydrazinolysis	IVa:	IM hydrazinium hydrate in pyridine/ glacial acetic acid/ water (4:3:0.35,v/v), pH 5.4
		IVb:	0.5M hydrazinium hydrate in pyridine/ glacial acetic acid/ water (4:1:0.25, v/v), pH 6.5

Numerous articles cited in the application teach the use of various protecting groups for protection of reactive functionalities and deprotection reagents and conditions in solid phase synthesis of combinatorial libraries. The working examples provided exemplify multiselective deprotection via sequence dependent preprogrammed selection of appropriate nucleotide building blocks to create oligomers with predetermined modifications, various combinations of which can generate a combinatorial set of molecules.

Conclusion

In light of the scope of the claims, the teachings in the specification, the high level of skill of those in this art, and the extensive knowledge of those of skill in this art, it would not require undue experimentation for a person of skill in the art to select blocking groups to block reactive moieties wherein at least 3 blocking groups are removable under at least 3 different conditions that are within scope of the instant claims, and subsequently derivatize the reactive moieties to generate the claimed combinatorial libraries of nucleotides or nucleosides. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter .

Public Policy Considerati ns

Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. In the above-captioned application, Applicant discloses to the public generation of combinatorial libraries of oligonucleotides by using various blocking groups to block the reactive moieties in the monomer building blocks, removing the blocking groups in a selective orthogonal fashion and optionally derivatizing the resulting reactive moieties. The blocking groups disclosed in the application can be replaced by other groups that are shown herein, extensively described in the literature and well-known to those of skill in the art. The conditions for orthogonal deprotection are described in the application. Therefore, it would be unfair, unduly limiting and contrary to the public policy upon which the U.S. patent laws are based to require applicant to limit the claims only to the specifically exemplified blocking groups and deblocking conditions. See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts".
>
> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require applicant to limit the claims to only the exemplified set of blocking groups and deprotecting conditions would permit those of skill in the art to readily create combinatorial libraries similar to those disclosed in the instant application, by replacing the blocking groups with other blocking groups using routine methods to practice what is disclosed in the application, but avoid infringing such limited claims. The instant application teaches the generation of combinatorial libraries of oligonucleotides blocking the reactive moieties in the

monomers with various protecting groups. Non-limiting examples of protecting groups for use in generation of the combinatorial libraries include, for example, trityl group used as a OH protecting group; β-cyanoethyl group as a phosphate protecting group and npe/npeoc groups base protecting groups. The disclosure thereby provides a means for others to produce combinatorial libraries of oligonucleotides by using any other orthogonal blocking groups for the reactive moieties. Restricting the process to using only the specific protecting groups described in the exemplary embodiment would permit one of skill in the art to make similar libraries using the disclosure of the application and routine protecting and deprotecting groups, but avoid infringing the claim.

Furthermore, as noted above, the first paragraph of §112 does not require a specific example of everything within the scope of a claim. In re Anderson, 471 F.2d 1237, 176 USPQ 331, 333 (CCPA 1973). Rather, it requires only that the disclosure be sufficient to teach one of skill in the art how to make and use the claimed subject matter without undue experimentation. As discussed above, the specification describes in detail, an exemplary embodiment wherein a combinatorial library of oligonucleotides is generated by blocking the reactive moieties in the monomers with trityl, β-cyanoethyl and npe/npeoc as protecting groups and orthogonally removing the protecting groups. Based on the specification disclosure and routine protecting group chemistry, one of skill in the art can practice the method as claimed without undue experimentation.

Further, a patentee not only is entitled to narrow claims particularly directed to a specific embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). There is no requirement for disclosure of every species within a genus. In this instance, the specification discloses a general scheme for preparing combinatorial libraries using known protecting groups and deprotecting conditions. The general scheme in application demonstrates use of a set of protecting groups and deprotecting conditions. As mentioned above, applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which

the applicant has disclosed.

Having provided the instant application, others can readily generate the combinatorial libraries of oligonucleotides using the methods as presently claimed. It would, therefore, be unduly limiting to restrict the claims to the specific protecting groups exemplified.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 24743-2302US
Address all correspondence to:
Stephanie L. Seidman, Esq.
HELLER EHRMAN WHITE & McAULIFFE
4350 La Jolla Village Drive, 7th Floor
San Diego, California 92122-1246
Telephone: 858 450-8400
Facsimile: 858 587-5360
email:sseidman@HEWM.com